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The Impact of Low Serum Sodium on Treatment Outcome of Targeted Therapy in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Cancer Database Consortium

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Abstract

Background—Hyponatremia has been associated with poor survival in many solid tumors and more recently found to be of prognostic and predictive value in metastatic renal cell cancer (mRCC) patients treated with immunotherapy.

Objective—To investigate the influence of baseline hyponatremia in mRCC patients treated with targeted therapy in the International Metastatic Renal Cell Carcinoma Database Consortium.

Design, setting, and participants—Data on 1661 patients treated with first-line vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) targeted therapy for mRCC were available from 18 cancer centers to study the impact of hyponatremia (serum sodium level <135 mmol/l) on clinical outcomes.

Outcome measurements and statistical analysis—The primary objective was overall survival (OS) and secondary end points included time to treatment failure (TTF) and the disease control rate (DCR). The chi-square test was used to compare the DCR in patients with and without hyponatremia. OS and TTF were estimated with the Kaplan-Meier method and differences between groups were examined by the log-rank test. Multivariable logistic regression (for DCR) and Cox regression (for OS and TTF) were undertaken adjusted for prognostic risk factors.

Results and limitations—Median OS after treatment initiation was 18.5 mo (95% confidence interval [CI], 17.5–19.8 mo), with 552 (33.2%) of patients remaining alive on a median follow-up of 22.1 mo. Median baseline serum sodium was 138 mmol/l (range: 122–159 mmol/l), and hyponatremia was found in 14.6% of patients. On univariate analysis, hyponatremia was associated with shorter OS (7.0 vs 20.9 mo), shorter TTF (2.9 vs 7.4 mo), and lower DCR rate (54.9% vs 78.8%) ($p < 0.0001$ for all comparisons). In multivariate analysis, these effects remain

significant (hazard ratios: 1.51 [95% CI, 1.26–1.80] for OS, and 1.57 [95% CI, 1.34–1.83] for TTF; odds ratio: 0.50 [95% CI, 34–0.72] for DCR; adjusted $p < 0.001$). Results were similar if sodium was analyzed as a continuous variable (adjusted $p < 0.0001$ for OS, TTF, and DCR).

Conclusions—This is the largest multi-institutional report to show that hyponatremia is independently associated with a worse outcome in mRCC patients treated with VEGF- and mTOR-targeted agents.

Keywords

Hyponatremia; Renal cell cancer; Anti-VEGF; Prognostic factors

1. Introduction

Renal cell cancer (RCC) is the sixth most common cancer in United States [1], accounting for an estimated 64 770 new cases and 13 570 deaths in 2012. Patients can present with metastatic disease or recur after nephrectomy. Currently, patients with advanced RCC are stratified into three different risk groups based on the two prognostic models used most [2,3]. These prognostic models take into account several baseline clinical and laboratory values, and capture the natural history of metastatic RCC (mRCC).

Hyponatremia is one of the most common electrolyte disorders observed in hospitalized patients [4], and it is probably highly underestimated. According to the studied populations and the definition of hyponatremia, its reported frequency varies greatly, from <1% to >40% [5]. Hyponatremia can be caused by either dilution of the serum sodium by excess retained free water or by excessive sodium losses.

Hyponatremia has been associated with poor survival in several nonmalignant diseases, such as congestive heart failure, liver cirrhosis, and infectious diseases (pneumonia, childhood meningitis, necrotizing soft-tissue infection) [6–8]. Serum sodium has been analyzed in mRCC patients treated with cytokines [9], and hyponatremia was found to be associated with a worse outcome. Similar observations have been made in malignancies, such as advanced hepatocellular carcinoma [10], advanced gastric cancer [11], advanced small cell lung cancer [12], and localized RCC [13]. However, the role of hyponatremia in mRCC patients treated with targeted therapies is not well defined. One study including 87 mRCC patients treated with sunitinib or sorafenib showed that hyponatremia was significantly associated with cancer-specific survival [14]. Since serum sodium levels are routinely measured and, therefore, widely available most of the time, we sought to investigate the association of hyponatremia on treatment outcomes in mRCC patients treated with contemporary targeted therapies.

2. Methods

2.1. Patient population

The International Metastatic Renal Cell Cancer Database Consortium (IMDC) includes 20 academic cancer centers from Canada, the United States, Japan, South Korea, Singapore, and Denmark. As of October 10, 2012, a total of 2370 patients who had received first-line

targeted therapy between 2003 and 2012 were included. For this study, 1661 patients from 18 centers had baseline serum sodium level information readily available.

All patients were diagnosed with mRCC of any pathologic subtype with no prior vascular endothelial growth factor (VEGF)-targeted therapy. Prior treatment with immunotherapy (interleukin-2 or interferon) was allowed. The majority of patients were treated with a first-line anti-VEGF agent: sunitinib, sorafenib, axitinib, bevacizumab, pazopanib, or tivozanib; and a small proportion of patients were treated with mammalian target of rapamycin (mTOR)-targeted agents: temsirolimus and everolimus.

Baseline demographic, clinical, and laboratory data, including those previously found to have prognostic value, were collected retrospectively on all patients by using uniform database templates to ensure consistent data collection [2]. Laboratory values were standardized against institutional upper limit of normal (ULN) and lower limit of normal (LLN) values when appropriate. Hyponatremia was defined as a serum sodium level <135 mmol/l, which is a widely used laboratory cut point. Outcome data on response rate, time to treatment failure (TTF), and overall survival (OS) were collected from patient charts. This study received institutional review board approval from each participating center.

2.2. Statistical analysis

The primary objective was to investigate whether baseline hyponatremia was associated with OS, and secondary end points included TTF and the disease control rate (DCR). OS was defined as time between targeted therapy initiation and the date of death, or it was censored at the date of the last follow-up visit. TTF was defined as time between treatment initiation and progression, drug cessation, death, or it was censored at the last follow-up visit. Progression was determined according to clinical criteria that made continuation of treatment impossible or radiographic criteria using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. DCR included complete response, partial response, and stable disease to targeted therapy per the RECIST criteria, which has been used as an inverse measure of refractory disease (progressive disease as best response).

Patient and tumor characteristics, and DCR were compared between patients with and without hyponatremia using the chi-square test. OS and TTF were estimated with the Kaplan-Meier method and differences between groups were examined by the log-rank test. Multivariable logistic regression (for DCR) and Cox regression (for OS and TTF) were undertaken, adjusted for the IMDC prognostic risk factors [2]. Subgroup analyses were performed according to the IMDC favorable-, intermediate-, and poor-risk groups, respectively. Serum sodium level was also analyzed as a continuous variable in both univariate and multivariable models adjusted for the IMDC prognostic risk factors.

All statistical computations were performed using SAS v.9.2 (SAS Institute Inc., Cary, NC, USA) and a p value (two-sided) <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Patient and disease characteristics at the initiation of targeted therapy, both of all patients (*n* = 1661) and separated by hyponatremia status, are presented in Table 1. Most patients were male (74%). Fifty-three percent of patients were older than 60 yr. The majority of patients had clear cell histology (89%). Patients received one of the following VEGF-targeted therapies: sunitinib (75%), sorafenib (17%), bevacizumab (4%), pazopanib (2%), tivozanib (<1%), or axitinib (<1%); or mTOR-targeted therapies: temsirolimus (2%) and everolimus (<1%). At the time of data analysis, 1428 patients (86%) had stopped the first-line targeted therapy, and the median time on the first-line targeted therapy was 6.5 mo (range: 0.1–79.5 mo). The median OS after targeted treatment initiation was 18.5 mo (95% CI, 17.5–19.8 mo), with 552 patients (33.2%) remaining alive at last follow-up. The median follow-up time for patients still alive was 22.1 mo (interquartile range: 10.8–37.3 mo).

A total of 243 patients (14.6%) had hyponatremia (baseline serum sodium level <135 mmol/l) at the initiation of targeted therapy. The median serum sodium level of the patient population was 138 mmol/l (range: 122–159 mmol/l). Patients who had hyponatremia more likely had low Karnofsky performance status (KPS) scores (<80) ($p < 0.0001$), sarcomatoid pathology ($p = 0.004$), time from diagnosis to targeted therapy <1 yr ($p = 0.001$), time from diagnosis to metastatic disease <1 yr ($p = 0.006$), low hemoglobin level ($p < 0.0001$), high serum calcium level ($p < 0.0001$), elevated level of lactate dehydrogenase (LDH) ($p = 0.001$), high neutrophil levels ($p < 0.0001$), and high platelet count ($p < 0.0001$); but less likely to have had prior nephrectomy or immunotherapy ($p < 0.05$) (Table 1).

3.2. Overall survival

When evaluating OS, we observed that patients with baseline hyponatremia had a significantly shorter median OS compared to patients with normal serum sodium levels (7.0 vs 20.9 mo; hazard ratio [HR]: 2.31; 95% CI, 1.97–2.71; $p < 0.0001$) (Fig. 1A). After adjusting for the IMDC prognostic risk factors, these results remained statistically significant (adjusted HR: 1.51 [95% CI, 1.26–1.80; $p < 0.0001$]) (Table 2). Subgroup analysis according to the IMDC risk groups showed that hyponatremic patients in the intermediate- or poor-risk group had a significantly shorter median OS compared to patients with normal serum sodium levels (10.9 vs 23.5 mo and 5.1 vs 10.0 mo, respectively) (HR: 1.80 [95% CI, 1.37–2.37; $p < 0.0001$] and 1.60 [95% CI, 1.29–1.99; $p < 0.0001$], respectively). Patients in the favorable-risk group with or without hyponatremia had median OS of 24.3 versus 41.1 mo, respectively (HR: 1.11 [95% CI, 0.45–2.71]), and this difference was not statistically significant ($p = 0.826$) (Table 2). Of note, there were only 10 patients with hyponatremia in the favorable group.

3.3. Time to treatment failure

Patients with baseline hyponatremia had also a significantly shorter median TTF compared to patients with normal baseline serum sodium levels (2.9 vs 7.4 mo; HR: 1.96 [95% CI, 1.70–2.26; $p < 0.0001$]) (Fig. 1B). These results remained statistically significant after adjusting for the IMDC risk factors on multivariate analysis (adjusted HR: 1.57 [95% CI,

1.34–1.83; $p < 0.0001$]). Patients in the favorable-risk group with or without hyponatremia had similar median TTF (12.7 vs 11.7 mo; HR: 1.16 [95% CI, 0.61–2.20; $p = 0.644$]). However, in the intermediate- and poor-risk groups, hyponatremic patients had a significantly shorter median TTF when compared to patients with normal serum sodium level (4.1 vs 7.9 mo for the intermediate-risk group; and 2.3 vs 4.5 mo for the poor-risk group) (HR: 1.69 [95% CI, 1.34–2.14; $p < 0.0001$] and 1.63 [95% CI, 1.32–2.01]; $p < 0.0001$], respectively) (Table 2).

3.4. Disease control rate

The associations between baseline serum sodium level and treatment response to targeted therapy using RECIST criteria showed that hyponatremia was significantly associated with a lower DCR. A total of 1320 (79%) patients were available for this analysis: 175 had hyponatremia and 1145 had normal serum sodium levels. Patients with baseline hyponatremia had a DCR of 55% compared to 79% in patients without hyponatremia (odds ratio [OR]: 0.33 [95% CI, 0.24–0.46; $p < 0.0001$]) (Table 2). These results remained statistically significant after adjusting for the IMDC risk factors (adjusted OR: 0.50 [95% CI, 0.34–0.72; $p = 0.0003$]). Patients with hyponatremia also showed a reduced DCR compared to patients with normal serum sodium level in each of the IMDC favorable, intermediate, and poor groups (OR: 0.18 [95% CI, 0.04–0.79], 0.47 [95% CI, 0.27–0.80], and 0.48 [95% CI, 0.29–0.78], respectively; $p < 0.05$).

3.5. Serum sodium concentration as a continuous variable

Baseline serum sodium level was an independent predictor of OS, TTF, and DCR when it was analyzed as a continuous variable (Table 3). After covariate adjustment, the HR associated with each 3-mmol/l decrease in serum sodium concentration was 1.19 (95% CI, 1.12–1.26) for mortality and 1.20 (95% CI, 1.14–1.27) for TTF ($p < 0.0001$). Decreased serum sodium level was also related with a poorer DCR (adjusted OR: 0.77 [95% CI, 0.68–0.87] per 3-mmol/l decrease; $p < 0.0001$). Results were also similar in subgroup analysis according to the IMDC risk groups and when sodium level was analyzed as a continuous or categorical variable (hyponatremia: yes or no).

4. Discussion

To our knowledge, this is the largest study to evaluate the association of hyponatremia on outcome of mRCC patients treated with targeted agents. Hyponatremia was found to be associated with a significant lower OS, TTF, and DCR at first staging evaluation in mRCC patients receiving targeted therapy. Hyponatremic patients had 57% and 51% increase in the risk of treatment failure or death, respectively. In addition, the 50% reduction in the odds of disease control according to RECIST criteria suggests that patients with baseline hyponatremia are more likely to be primary refractory to targeted therapy, suggesting an aggressive underlying biology, or a poor tolerance to therapy leading to targeted therapy dose reduction. Baseline hyponatremia was associated with other baseline unfavorable prognostic features included in currently available prognostic scores (IMDC and Memorial Sloan-Kettering Cancer Center), such as low KPS scores, time from diagnosis to targeted therapy treatment <1 yr, low hemoglobin level, high serum calcium level, elevated LDH,

high neutrophil levels, and high platelet count. However, it is important to point out that it remained statistically significant even after adjusting for these known prognostic risk factors, which captures the natural history and different survival patterns of mRCC patients treated with targeted agents.

Hyponatremia has been shown to be a poor prognostic marker in a number of different diseases, including liver cirrhosis, congestive heart failure (CHF), systemic infections, and certain malignancies. In patients with end-stage liver disease, hyponatremia was related to hemodynamic derangement, and was important in the potential development of hepatorenal syndrome [15,16]. Based on this, sodium levels are included in the Model for End-Stage Liver Disease score for the determination of liver transplant allocation [6].

Hyponatremia has also shown to be important in patients with CHF. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, patients with persistent hyponatremia had a significantly increased risk of all-cause mortality, rehospitalization from heart failure, and death [17]. Hyponatremia, along with a combination of volume overload, water retention, and increased neurohormonal activation, are thought to underlie the poor prognosis in these patients.

The presence of hyponatremia has also been shown to influence the prognosis of patients with systemic infections, including pulmonary [7], cerebral, and necrotizing soft tissue infections [18]. It is thought that inappropriate antidiuretic hormone (ADH) levels may be partly responsible for the altered serum sodium levels. Progression of localized infection in sepsis causes an increase in ADH level as well as adrenocortical insufficiency, resulting in hyponatremia [19].

The mechanisms underlying the development of hyponatremia specifically in RCC patients remains unclear. ADH may play a role as in other cancers [12], usually from an ectopic production (syndrome of inappropriate antidiuretic hormone [SIADH]), although it can also be a marker of burden of disease. SIADH is most commonly found in patients with lung cancer (11–15%) [20], head and neck cancer (approximately 3%) [21], breast cancer, and, to a lesser extent, in other types of malignancies. However, it is also possible to speculate that patients with RCC may have some degree of renal dysfunction, especially those submitted to nephrectomy, that could lead to hyponatremia. Cerebral salt wasting can also be involved in the hyponatremia in cancer patients. This condition is most commonly seen in patients with intracranial tumors that could impair the neurohypophysial pathways, resulting in increased secretion of brain or atrial natriuretic peptides, which can lead to an inappropriate increased renal excretion of sodium [22].

The incidence of hyponatremia in a general cancer population seems to be lower than that observed in our mRCC patient population. In a series from Institut Jules Bordet, a hyponatremia incidence of 3.7% was reported in patients with different types of malignancies [5], whereas the incidence of hyponatremia in our mRCC cohort was 15%. This difference could be partly explained by the mild renal impairment in mRCC patients, since a significant proportion of them have undergone nephrectomy. Another possibility is the more advanced stage in our cohort. Cancer patients with hyponatremia have also been

shown to have an increased mortality compared to those with normal serum sodium levels [5]. There is some evidence suggesting that the presence of hyponatremia in patients with hepatocellular carcinoma is associated with a poorer prognosis with liver transplantation [10]. A recent study examined the role of hyponatremia in the treatment of advanced gastrointestinal stromal tumors with tyrosine-kinase inhibitor (imatinib) [23]. The authors reported that low serum sodium at the start of imatinib treatment was a possible adverse prognostic factor affecting OS. One of the largest series in a general cancer population showed that hyponatremia was associated most commonly with altered ADH levels, which could be secondary to a volume depletion, diuretic use, renal failure, or hypotonic fluid intake [5]. Paraneoplastic syndromes, such as small cell lung cancers, are commonly associated with ADH secretion [12]. Hyponatremia can also be a consequence of cancer therapy or its side effects, such as diarrhea and vomiting [24]. However, in our patient population, the cancer therapy probably did not play a role since the hyponatremia was observed at baseline.

Our data demonstrate that hyponatremia in mRCC patients treated with anti-VEGF agents had poor prognosis compared to patients with baseline normal serum sodium levels. These data are in agreement with a British study in which a low preoperative sodium concentration was found to be associated with reduced survival in patients with RCC undergoing nephrectomy [13]. In our study, we have observed that hyponatremia was present in 15% of patients at baseline. Similarly, another recent study, including only mRCC patients treated with cytokines (two cohorts of 120 patients each), showed that hyponatremia was present in 14–20% of patients. In this same study, the authors observed that hyponatremic patients had lower survival in multivariate analysis. Furthermore, hyponatremia was associated with lack of response (by RECIST) to cytokines [9].

Hyponatremia in patients with mRCC could be also just a reflection of the baseline comorbidities, such as renal failure, although prior data from our group showed that renal function at therapy initiation does not adversely affect the efficacy of targeted therapy in advanced RCC [25]. Several other comorbidities or factors may impair sodium homeostasis such as ethnicity, CHF, hypertension, diabetes, cirrhosis, adrenal insufficiency, hypothyroidism, diuretics, steroids, antiepileptics, selective serotonin reuptake inhibitors, or alcohol use [26].

Our study has some limitations, which include the retrospective nature of our study and the lack of evaluation of hyponatremia after starting the treatment for mRCC with targeted therapy. It is unknown if aggressive treatment of baseline hyponatremia could eventually alter the outcome of RCC patients treated with targeted therapy. Although hyponatremia was prognostic, we could not determine if it was a predictive biomarker since all patients with mRCC were treated with targeted therapies. Furthermore, we could not adjust our analysis for other baseline factors potentially affecting sodium homeostasis; neither could we evaluate the association with dose reductions of targeted agents. The strengths of our study include the large number of included patients and the adjustment for the IMDC prognostic risk criteria.

5. Conclusions

In conclusion, we have shown that, in mRCC patients treated with targeted therapy, baseline hyponatremia is associated with a poorer OS, TTF, and DCR. Hyponatremia may be a quick and efficient method of stratifying patients beyond the IMDC criteria. Hyponatremia deserves to be further investigated as a prognostic factor and evaluated for inclusion in future prognostic tools.

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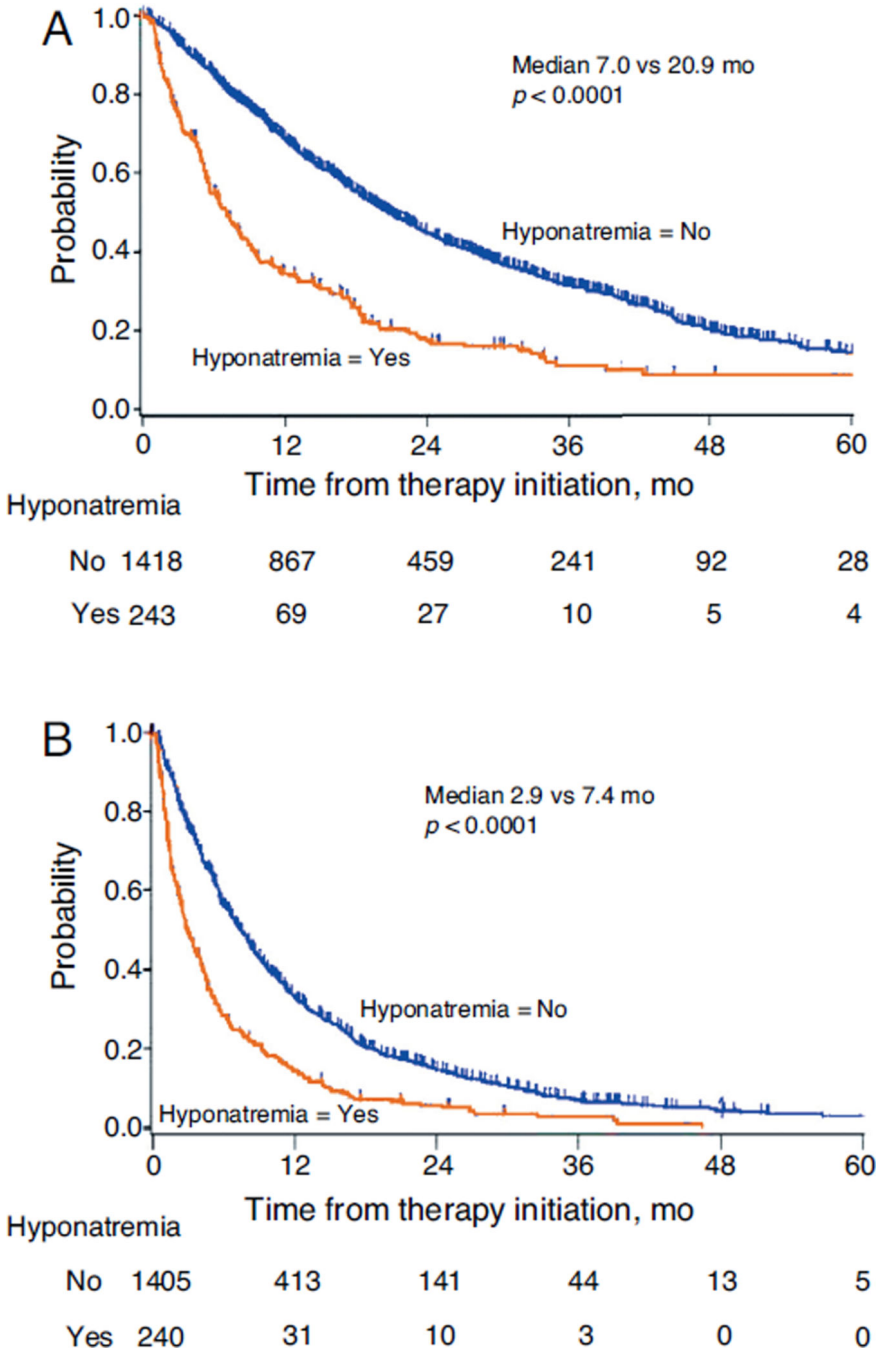

Fig. 1.

Kaplan-Meier plots of (A) overall survival and (B) time to treatment failure by hyponatremia at the initiation of targeted therapy.

Table 1

Patient and disease characteristics at the initiation of targeted therapy

	All patients (*N* = 1661)		Hyponatremia (serum sodium level <135 mmol/l)				
			Yes (*n* = 243)		No (*n* = 1418)		*p* value
	No.	%	No.	%	No.	%	
Age at therapy initiation, yr							
<60	778	47	113	47	665	47	
≥60	883	53	130	53	753	53	NS
KPS score							
≥80	1220	75	125	53	1095	79	
<80	410	25	111	47	299	21	<0.0001
Sex							
Female	427	26	70	29	357	25	
Male	1225	74	172	71	1053	75	NS
Metastases, no.							
1	478	29	62	26	416	29	
>1	1183	71	181	74	1002	71	NS
Histology							
Clear cell histology	1396	89	197	87	1199	89	
Non–clear cell histology	180	11	29	13	151	11	NS
Sarcomatoid pathology							
No	1367	91	184	86	1183	92	

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	All patients (*N* = 1661)		Hyponatremia (serum sodium level <135 mmol/l)				
			Yes (*n* = 243)		No (*n* = 1418)		*p* value
	No.	%	No.	%	No.	%	
Yes	137	9	31	14	106	8	0.004
Prior nephrectomy							
No	391	24	85	35	306	22	
Yes	1270	76	158	65	1112	78	<0.0001
Prior immunotherapy							
No	1276	77	202	83	1074	76	
Yes	385	23	41	17	344	24	0.012
Diagnosis to TKI therapy <1 yr							
No	734	44	82	34	652	46	
Yes	925	56	159	66	766	54	0.001
Diagnosis to metastasis <1 yr							
No	490	30	53	22	437	31	
Yes	1156	70	185	78	971	69	0.006
Low hemoglobin level							
No	659	40	51	21	608	43	
Yes	995	60	191	79	804	57	<0.0001
Hypercalcemia							
No	1454	90	180	77	1274	92	

	All patients (*N* = 1661)		Hyponatremia (serum sodium level <135 mmol/l)				
			Yes (*n* = 243)		No (*n* = 1418)		*p* value
	No.	%	No.	%	No.	%	
Yes	168	10	55	23	113	8	<0.0001
Elevated LDH (>1.5 ULN)							
No	997	85	133	76	864	87	
Yes	175	15	41	24	134	13	0.001
Neutrophilia (>ULN)							
No	1349	85	161	69	1188	87	
Yes	242	15	72	31	170	13	<0.0001
Thrombophilia (>ULN)							
No	1334	81	154	64	1180	84	
Yes	319	19	88	36	231	16	<0.0001

NS = not significant; KPS = Karnofski performance status; LDH = lactate dehydrogenase; TKI = tyrosine kinase inhibitor; ULN = upper limit of normal.

Table 2

Associations of hyponatremia with overall survival, time to treatment failure, and disease control rate in all patients who were treated with targeted therapy and in subgroup analysis according to the International Metastatic Renal Cell Cancer Database Consortium risk groups

	All patients (*N* = 1661)	According to the IMDC risk groups*		
		Favorable (*n* = 261)	Intermediate (*n* = 870)	Poor (*n* = 461)
	Hyponatremia Yes/No	Hyponatremia Yes/No	Hyponatremia Yes/No	Hyponatremia Yes/No
OS				
No.	243/1418	10/251	88/782	137/324
Median, mo	7.0/20.9	24.3/41.1	10.9/23.5	5.1/10.0
Log-rank *p* value	<0.0001	0.826	<0.0001	<0.0001
HR (95% CI)	2.31 (1.97–2.71)	1.11 (0.45–2.71)	1.80 (1.37–2.37)	1.60 (1.29–1.99)
Adjusted HR** (95% CI)	1.51 (1.26–1.80)	–	–	–
Adjusted *p* value**	<0.0001	–	–	–
TTF				
No.	240/1405	10/250	87/775	135/320
Mo, median	2.9/7.4	12.7/11.7	4.1/7.9	2.3/4.5
Log-rank *p* value	<0.0001	0.644	<0.0001	<0.0001
HR (95% CI)	1.96 (1.70–2.26)	1.16 (0.61–2.20)	1.69 (1.34–2.14)	1.63 (1.32–2.01)
Adjusted HR** (95% CI)	1.57 (1.34–1.83)	–	–	–
Adjusted *p* value**	<0.0001	–	–	–
DCR				
No.	175/1145	9/205	66/641	93/244
No. (%) with CR plus PR plus SD	96(55)/902(79)	6(67)/188(92)	42(64)/506(79)	46(49)/164(67)
Chi-square *p* value	<0.0001	0.023	0.005	0.003
OR (95% CI)	0.33 (0.24–0.46)	0.18 (0.04–0.79)	0.47 (0.27–0.80)	0.48 (0.29–0.78)
Adjusted OR** (95% CI)	0.50 (0.34–0.72)	–	–	–

	All patients (*N* = 1661)	According to the IMDC risk groups*		
		Favorable (*n* = 261)	Intermediate (*n* = 870)	Poor (*n* = 461)
	Hyponatremia Yes/No	Hyponatremia Yes/No	Hyponatremia Yes/No	Hyponatremia Yes/No
Adjusted *p* value**	0.0003	–	–	–

CI = confidence interval; CR = complete response; DCR = disease control rate; HR = hazard ratio; IMDC = International Metastatic Renal Cell Cancer Database Consortium; OR = odds ratio; OS = overall survival; PR = partial response; SD = stable disease; TTF = time to treatment failure.

* Exclude 69 patients with an unknown risk group.

** Adjusted for the IMDC prognostic risk factors (time from diagnosis to targeted therapy <1 yr, Karnofsky performance status score <80, anemia, neutrophilia, thrombocytosis, hypercalcemia).

Table 3

Associations of serum sodium concentration as a continuous variable with overall survival, time to treatment failure, and the disease control rate in all patients and in subgroup analysis according to the International Metastatic Renal Cell Cancer Database Consortium risk groups

	OS		TTF		DCR	
	HR* (95% CI)	*p* value	HR* (95% CI)	*p* value	OR* (95% CI)	*p* value
All patients						
Univariable model	1.37 (1.29–1.44)	<0.0001	1.29 (1.23–1.35)	<0.0001	0.66 (0.59–0.74)	<0.0001
Multivariable model**	1.19 (1.12–1.26)	<0.0001	1.20 (1.14–1.27)	<0.0001	0.77 (0.68–0.87)	<0.0001
By IMDC risk groups						
Favorable	1.02 (0.85–1.22)	0.842	1.00 (0.87–1.16)	0.962	0.75 (0.48–1.18)	0.216
Intermediate	1.27 (1.17–1.39)	<0.0001	1.23 (1.15–1.32)	<0.0001	0.76 (0.64–0.90)	0.001
Poor	1.23 (1.13–1.33)	<0.0001	1.27 (1.17–1.37)	<0.0001	0.70 (0.58–0.84)	0.0002

DCR = disease control rate; HR = hazard ratio; IMDC = International Metastatic Renal Cell Cancer Database Consortium; OR = odds ratio; OS = overall survival; TTF = time to treatment failure.

* HR or OR is presented as a relative risk per 3-mmol/l decrease in the serum sodium concentration.

** Adjusted for the IMDC prognostic risk factors (time from diagnosis to treatment, Karnofsky performance status score <80, low hemoglobin level, neutrophilia, thrombocytosis, hypercalcemia).